

## Six-city study of treatment of gonorrhoea in men using single oral doses of 1·5 or 3 g. tetracycline hydrochloride

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One of the most effective, safe, simple, and inexpensive forms of therapy for gonorrhoea has been the single oral dose of tetracycline. In 1967, a study of 141 male patients with gonococcal urethritis treated at the Fulton County Health Department, Atlanta, Georgia, with a single oral dose of 1·5 g. oxytetracycline hydrochloride showed a cure rate of approximately 94 per cent. (McLone, Kiley, and Hackney, 1967). The authors concluded that tetracycline might become the drug of choice in the therapy of gonorrhoea. By the latter half of 1968 in Atlanta, however, it was the author's impression that this dosage of tetracycline no longer yielded this previous high cure rate; an attempt was therefore made to test this empirical judgment.

It is difficult to assess the effectiveness of any drug in the therapy of gonorrhoea in a large country like the United States because there are so many different strains of the gonococcus with various degrees of resistance to different antibiotics (Sokoloff and Goldstein, 1963), and various geographical distributions (unpublished data of John E. Martin, Jr., Supervisory Research Microbiologist, Venereal Disease Research Laboratory, National Communicable Disease Center, Atlanta, Georgia).

To evaluate the effectiveness of tetracycline hydrochloride (Panmycin, Upjohn)\* in single oral doses of 1·5 and 3 g. in cases of acute gonococcal urethritis in men, a simultaneous cooperative study of the drug was undertaken in six geographically separated metropolitan areas: Atlanta, Georgia; Dallas, Texas; Memphis, Tennessee; New York City, New York; Norfolk, Virginia; and San Francisco, California.

### Methods and Material

The study was carried out during the first 6 months of 1969. Approximately 100 male patients with uncomplicated gonococcal urethritis were selected from each of

the six cities. They were diagnosed at Fulton County Health Department, Atlanta, Georgia; Wahoo Park Clinic, Dallas, Texas; Shelby County Health Department, Memphis, Tennessee; Norfolk City Health Department, Norfolk, Virginia; San Francisco City Clinic, San Francisco, California; and at the Chelsea and Morrisania Social Hygiene Clinics, New York City.

The diagnosis of gonococcal urethritis depended on a frank purulent discharge, showing Gram-negative intracellular diplococci with the typical morphology of *Neisseria gonorrhoeae*.

Approximately one-half the patients were treated with a single oral dose of 1·5 g. tetracycline hydrochloride and the remaining patients received twice this amount. The dosage was allocated on a random basis.

Therapeutic evaluation was performed 48 to 72 hrs after treatment. Intraurethral scrapings were taken with a sterile platinum wire loop and specimens were inoculated directly onto Thayer-Martin selective medium (Thayer and Martin, 1964). These cultures were incubated at 34·5°C. in an atmosphere of 2 per cent. carbon dioxide and examined at 24 to 48-hr intervals. Demonstration of Gram-negative oxidase-positive colonies was considered diagnostic of the presence of the gonococcus. In addition, smears were prepared with specimens from patients with urethral exudates. If Gram-negative diplococci were noted, the case was considered to be a treatment failure and another form of therapy was given.

Any patient admitting exposure to risk of infection after treatment whose urethral specimen yielded a positive culture was excluded from the study.

At the post-treatment evaluation, complications of therapy were noted, special attention being paid to cutaneous and gastrointestinal signs and symptoms. Only one complication was recorded for each patient, symptoms being rated in a descending order: vomiting, diarrhoea, nausea, abdominal pain, and dizziness. Any patient reporting more than one sign or symptom was credited with whichever came highest in the scale. This system was used to simplify the interpretation of data. Vomiting patients usually experienced nausea, but were not among the group that reported nausea as a major symptom.

### Results

The results of this study are summarized in Table I. The cure rate is calculated on the basis of the number

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of patients returning for follow-up investigation. This tends to weight the results towards a higher failure rate, but this has been the traditional method in studying the therapy of gonorrhoea. The overall cure rate for the patients treated with 1.5 g. was 84 per cent. and for those given 3g. it was 91 per cent.

The complications are presented in Table II. Vomiting occurred in nineteen patients, five of whom had received only 1.5 g. tetracycline. Only one patient in the entire study, a patient in San Francisco, immediately vomited his medication so that parenteral therapy had to be substituted. Nausea,

TABLE I Results of tetracycline therapy in six-city study of 1.5 and 3 g. single oral dose in treatment of male gonococcal urethritis.

City	Dose (g.)	No. treated	No. returned	Result		
				Cure	Fail	Per cent. cured
Atlanta	1.5	51	30	26	4	87
	3.0	53	36	33	3	92
Dallas	1.5	75	50	42	8	84
	3.0	85	50	49	1	98
Memphis	1.5	59	43	40	3	93
	3.0	57	35	35	0	100
New York City	1.5	59	49	45	4	92
	3.0	59	50	50	0	100
Norfolk	1.5	76	69	59	10	86
	3.0	66	60	55	5	92
San Francisco	1.5	52	39	23	16	59
	3.0	50	41	35	6	85
Total	1.5	368	280	235	45	84
	3.0	370	272	257	15	95

TABLE II Complications in patients treated with single oral dose of 1.5 and 3 g. tetracycline HCl

City	Dose (g.)	No. returned	Complications					Per cent. with complications	Positive complication†
			Diarrhoea	Nausea	Vomiting	Dizziness	Abdominal pain		
Atlanta	1.5	30	1					3	1
	3.0	36	1	3		1		8	
Dallas	1.5	50		4				8	
	3.0	50		7	4	1		24	
Memphis	1.5	43		1	2			7	
	3.0	35		2	2			11	
New York City	1.5	49	1	3	2		2	16	
	3.0	50	6	12	6	1	1	52	
San Francisco	1.5	39		1	1			5	
	3.0	41	2	1	2*			12	1*

\*One patient vomited the drug immediately.

Note:

†Positive complication refers to treatment failure in patient experiencing a complication.

the symptom most commonly noted, was reported as a major symptom by 34 patients, eight of whom had received 1.5 g. In the group of patients who experienced upper gastrointestinal complications (excluding the patient from the San Francisco study), there were no treatment failures. No cutaneous complications were noted. No complications were reported in the Norfolk study.

### Discussion

An important aspect of the evaluation of any drug is the establishment of a valid cure. Testing the patient 48 to 72 hours after therapy is not ideal, as the antibiotic may suppress the infection so that the patient is asymptomatic and the number of organisms decreases so that a false negative culture is obtained. On the other hand, if the patient is to be tested at longer intervals, he frequently fails to return and one is also confronted with the problems of re-infection.

In the 43 drug studies carried out since 1961 at the Fulton County Health Department, Atlanta, Georgia (USPHS, 1969), it was found that if a patient had a negative culture 48 to 72 hours after therapy and does not return for further treatment in about 7 days he can be considered cured. In the present study none of the patients considered to be "cured" on the basis of the culture result at the 72-hr evaluation returned again during the first week.

In the six cities, 368 patients were treated with 1.5 g. and 370 with 3 g. The overall cure rates for the 280 and 272 patients who returned for observation were 84 and 95 per cent. respectively.

This difference of 11 per cent. is highly significant ( $P < 0.01$ ). The range in cure rates in the six cities for the 1.5 g. schedule was 59 to 93 per cent. and that for the 3 g. schedule 85 to 100 per cent. Although the differences in cure rates were significant ( $P < 0.05$ ) for only two of the cities (Dallas and San Francisco), the 3 g. dose gave the best results in all six cities. The 3 g. dosage is, as expected, more effective than the 1.5 g. dosage.

Applying a test of independence ( $\chi^2$ ), it was shown that San Francisco had a significantly lower cure rate than the other cities, and it was concluded that treatment effectiveness varies with location. This geographical variation of the effectiveness of tetracycline suggests the presence of marked regional differences in the resistance of the gonococcus to this drug. It emphasizes the need to investigate the effectiveness of a particular drug in a given area and not to rely on studies carried out in distant localities or in past years.

The decline in the cure rate from 94 to 87 per cent. which was noted in the Atlanta area with single oral doses of 1.5 g. tetracycline probably reflects a rising

resistance of the gonococcus to this drug. This 13 per cent. failure rate and other even higher rates observed in the Dallas, Norfolk, and San Francisco areas would certainly remove this dosage of tetracycline from a list of preferred treatments in these areas. One possible explanation for the high cure rates noted in Memphis and New York City is that penicillin has hitherto been extensively used to treat gonorrhoea in these areas, whereas in the other four regions physicians had already been using tetracycline. Strains that are less sensitive to tetracycline are thus less likely to arise in those areas where penicillin is employed. Gonococci partially resistant to penicillin do not show a marked degree of resistance to tetracycline (unpublished data of John E. Martin, Jr., Supervisory Research Microbiologist, Venereal Disease Research Laboratory, National Communicable Disease Center, Atlanta, Georgia).

The San Francisco area, however, where the highest failure rate to tetracycline was found, has also a greater proportion of strains of *N. gonorrhoeae* requiring a higher minimum inhibitory concentration of penicillin than any other metropolitan area in the United States. This association of partial resistance to penicillin with partial resistance to tetracycline conforms with the findings of Amies (1969). However, many penicillin resistant strains were found to be sensitive to tetracycline.

The wide variation in reported complications, as presented in Table II, could possibly be related to the interviewing techniques employed by the various investigators at the post-treatment session. In the group of nineteen patients who vomited after therapy, the only case of treatment failure was that of the patient who vomited immediately. Excluding the patients in Norfolk, Virginia, in whom no complications were recorded, only this one out of 596 patients suffered upper gastrointestinal complications that necessitated the administration of another drug. It was concluded that the nausea and vomiting did not affect the absorption of the tetracycline to the point that the drug was ineffective.

### Summary

A six-city study was carried out of the effectiveness of tetracycline in single oral dosages of 1.5 and 3 g. in the treatment of acute gonococcal urethritis in the male. Approximately 100 patients were treated in each area. Regional cure rates varied between 59 and 93 per cent. for the 1.5 g. dosage and between 85 and 100 per cent. for the 3 g. dosage. The latter, as expected, gave the best results. The incidence of complications varied considerably. Since a test of independence demonstrated that one city had a significantly lower cure rate than the rest, it was concluded

that therapeutic decisions should not rest upon studies carried out in different geographical areas and in bygone years. Each physician should investigate the effectiveness of a given therapy in the region of his own practice.

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## Étude, dans six villes, du traitement de la gonococcie masculine par doses uniques buccales de 1,5 ou 3g. de chlorydrate de tetracycline

### SOMMAIRE

Dans 6 villes, on a apprécié l'action de la tétracycline en doses orales uniques de 1,5 et 3 g. dans le traitement de l'urétrite gonococcique masculine aiguë. Environ 100 malades furent traités dans chaque région. Le pourcentage de guérison varia, selon les villes, de 59 à 93 pour la dose de 1,5 g. et de 85 à 100 pour la dose de 3 g. Cette dernière posologie, comme prévu, donna les meilleurs résultats. L'incidence des complications varia considérablement. Comme un test d'indépendance a montré que, dans une ville, le taux de guérison était plus bas, d'une manière significative, que pour les autres, on conclut que les décisions thérapeutiques ne doivent pas reposer sur des études conduites dans des régions géographiquement différentes et sur plusieurs années. Chaque médecin doit étudier l'action d'un traitement donné dans la région où il pratique.